Simple Aliphatic Compounds with several double and triple bonds

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Dissertation

Submitted for the

Degree of Doctor of Philosophy

to the

Philosophical Faculty Section II

of the

University of Zurich

by

RAMASWAMY, S.

of

Madras, India.

Approved by

Professor Dr. Paul Karrer

1953

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To My Loving Parents

ACKNOWLEDGEMENT

The practical work of this dissertation was carried out in the Institute of Chemistry, University of Zurich, under the direction of

Professor Dr. Paul Karrer

to whom I am deeply grateful for his valuable guidance and constant help.

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Theoretical

The naturally occurring polyacetylenes frequently possess ethylenic linkages in conjugation with a polyine chain and often carboxyl groups as well. For example, lachnophyllum ester and matricaria ester (compounds I and III) have been isolated from plants. Some of them possess antibiotic properties: nemotin and mycomycin. Many such compounds have also been synthesised. Acetylene is frequently used in synthetic work as a convenient and reactive unit for building up the required carbon skeleton. Also, advantage has been taken of the unique addition reactions of the triple bond in order, subsequently, to introduce functional groups.[1]

OCCURRENCE AND ISOLATION:

Marjorie Anchel[2] isolated a few compounds from culture liquids of Basidiomycetes, which have in common an ultraviolet absorption spectra in the region of 205–360 mμ. The absorption spectrum of the antibiotic nemotin suggests that it must have the $-C=C-C\equiv C-C\equiv C-$ grouping. Nemotin and nemotinic acid are highly unsaturated and unstable. They undergo alkali conversion probably representing a shift of double bonds to conjugated positions.[3] Russian chemists, Wiljams et al[4] isolated the highly unsaturated aliphatic cis-lachnophyllum ester from Lachnophyllum Gossypinum Bge. They established its structure as:

$$CH_3—CH_2—CH_2—C\equiv C—C\equiv C—CH=CH—COOCH_3 \qquad (I)$$

Sörensen[5] isolated several polyacetylenic compounds from a few genera of Compositae : for example, dehydromatricaria ester[5a] from Artemesia Vulgaris L.

$$CH_3—CH=CH—C\equiv C—C\equiv C—C\equiv C—COOCH_3 \qquad (II)$$

Matricaria ester was extracted from the flowers of Matricaria Inodora L.[5]

$CH_3—CH=CH—C\equiv C—C\equiv C—CH=CH—COOCH_3$ **(III)**

In 1947, Johnson and Burdon[6] isolated a highly unstable antibiotic from the elaboration products of Norcardia acidophilus. In 1952, its structure was deduced as 3,5,7,8-tridecatetraene-10,12-diynoic acid. It is called mycomycin: [7]

$HC\equiv C—C\equiv C—CH=C=CH—CH=CH—CH=CH—CH_2COOH$ **(IV)**

Mycomycin (IV) undergoes alkali conversion to the isomeric isomycomycin (V) at room temperature.

$CH_3—C\equiv C—C\equiv C—C\equiv C—CH=CH—CH=CH—CH_2COOH$ **(V)**

METHODS OF SYNTHESES:

In the laboratory, such polyacetylenes can be synthesised by polymerisation, self-addition, Grignard and Reformatsky reactions.

I. The *condensation* between epichlorhydrin and sodium acetylide in liquid ammonia gives the primary alcohol pentenynol (VI). The yield varies with the quantity of sodium acetylide employed, the maximum being 45%.[8] In a similar way, phenylacetylene yields 5-phenylpent-2-en-4-yn-l-ol but in 15% yield only.

$$HC\equiv C—Na + Cl—CH_2—\underset{\diagdown\,O\,\diagup}{CH}—CH_2 \longrightarrow HC\equiv C—CH=CH—CH_2OH \quad \textbf{(VI)}$$

Condensation between methyl chlorovinyl ketone and sodium acetylide yields chlorocarbinol (VII-a) which in the presence of dilute acids rearranges to give the very reactive aldehyde (VII).[17]

$$HC\equiv CNa + CH_3—CO—CH=CHCl \longrightarrow$$

$$HC\equiv C—\underset{\displaystyle OH}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}—CH=CHCl \longrightarrow HC\equiv C—\overset{\displaystyle CH_3}{\overset{|}{C}}=CH—CHO \quad \textbf{(VII)}$$

(VII-a)

II. (a) *Self-addition* takes place with higher olefins. This process can generally be reversed by heating:[9]

$$\begin{array}{l} CH_2{=}CH{-}C{\equiv}C{-}CH{=}CH_2 \\ \quad + \\ CH_2{=}CH{-}C{\equiv}C{-}CH{=}CH_2 \end{array} \longrightarrow \begin{array}{l} CH_2{=}CH{-}C{\equiv}C{-}CH{-}CH_2 \\ \qquad\qquad\qquad\quad | \quad | \\ CH_2{=}CH{-}C{\equiv}C{-}CH{-}CH_2 \end{array} \qquad \text{(VIII)}$$

(b) *Polymerisation* : Acetylene in the presence of cuprous and ammonium chloride, will add a second molecule of acetylene or a molecule of monosubstituted acetylene. The reaction makes possible the synthesis of substances containing both ethylenic and acetylenic linkages and when applied to acetylene itself, furnishes vinylacetylene and divinylacetylene, the former being the starting material for the preparation of one type of modern rubber substitute.[10]

$$HC{\equiv}CH + HC{\equiv}CH \longrightarrow CH_2{=}CH{-}C{\equiv}CH + HC{\equiv}CH$$
$$\longrightarrow CH_2{=}CH{-}C{\equiv}C{-}CH{=}CH_2 \qquad \text{(IX)}$$

III. *Oxidative coupling* : Conjugated diacetylenic glycols can also be prepared by the oxidative coupling of various types of ethynyl carbinols, using cuprous ammonium chloride as catalysts.[11] Conjugated ethynyl ethylenic carbinols like hexenynol have been oxidised:[12,13]

a) $2\ [CH_3{-}CHOH{-}CH{=}CH{-}C{\equiv}CH] \longrightarrow$

$$CH_3{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}CH{=}CH{-}C{\equiv}C{-}C{\equiv}C{-}CH{=}CH{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}CH_3 \qquad \text{(X)}$$

This glycol (X) yields, on hydrogenation, dodecane-2:11-diol.

b) $2\ [HC{\equiv}C{-}CH{=}CH{-}CH_2OH] \longrightarrow$

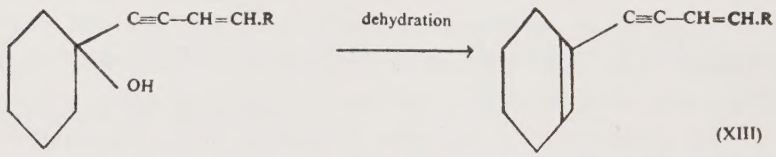
$$OHCH_2{-}CH{=}CH{-}C{\equiv}C{-}C{\equiv}C{-}CH{=}CH{-}CH_2OH \qquad \text{(XI)}$$

(c) Through the *asymmetric oxidative coupling*[5a] of pentyne-1 and penten-3-yn-1-ol-5, decene-2-diyn-4,6-ol-1 (XII) has been synthesised.

$$CH_3—CH_2—CH_2—C\equiv CH + HC\equiv C—CH=CH—CH_2OH \longrightarrow$$
$$CH_3—CH_2—CH_2—C\equiv C—C\equiv C—CH=CH—CH_2OH \qquad \textbf{(XII)}$$

Compound XII gives, on oxidation, lachnophyllum acid.

IV. *Dehydration* : Tertiary alcohols, obtained by the condensation of cyclohexanone with monosubstituted acetylene or vinylacetylene, can be dehydrated[14] with phosphorus oxychloride in pyridine to compounds containing the conjugated systems $C\equiv C—C=C$ and $C=C—C\equiv C—C=C$ respectively, in good yields.



(XIII)

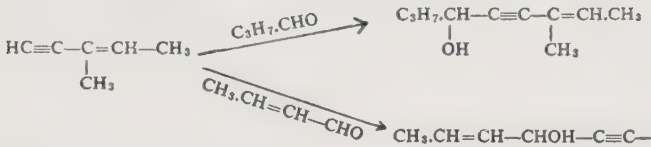
V. *Grignard and Reformatsky Reactions* : It is known that the most satisfactory method of condensing conjugated vinylacetylenes with aldehydes and ketones is by means of their Grignard compounds. Secondly, the Reformatsky type of condensation between cyclohexanone and propargyl bromide can also be extended to unsaturated aldhehydes and ketones in reactions with a variety of substituted propargyl bromides.[15] Karrer, Heilbron, Jones, Isler, Bohlmann and several others have synthesised various compounds containing acetylenic and ethylenic bonds by condensing the Grignard compounds of propargyl alcohol, methylpentenynol and similar compounds with various unsaturated aldehydes and ketones.

(a)[12]

$$R—CH=CH—CHO \xrightarrow{BrMgC\equiv C—CH_2OMgBr} R—CH=CH—CHOH—C\equiv C—CH_2OH$$
$$\xrightarrow{SOCl_2 \text{ \& Pyridine}} R—CHCl—CH=CH—C\equiv C—CH_2Cl \xrightarrow{NaNH_2}$$
$$R—CH=CH\,(C\equiv C)_2H \longrightarrow R—CH=CH\,(C\equiv C)nH$$

(XIV)

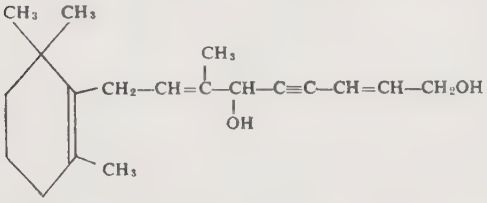
(b) Condensation with dimethylvinylacetylene :[16]



(XV-a)

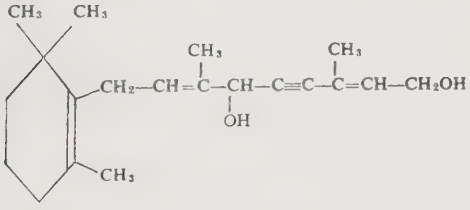
(XV-b)

(c) Heilbron et al[17] condensed pentenynol (VI) with the C_{14}aldehyde obtaining glycol (XVI) which, on partial hydrogenation and removal of water, yielded norvitamin A alcohol.

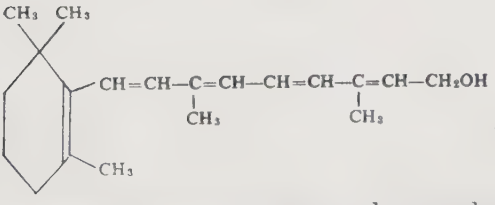


(XVI)

(d) Isler and collaborators[18] condensed C_{14}-aldehyde with methylpentenynol through the Grignard reaction and obtained the acetylenic carbinol (XVII), an intermediate product in the synthesis of vitamin A (XVIII):



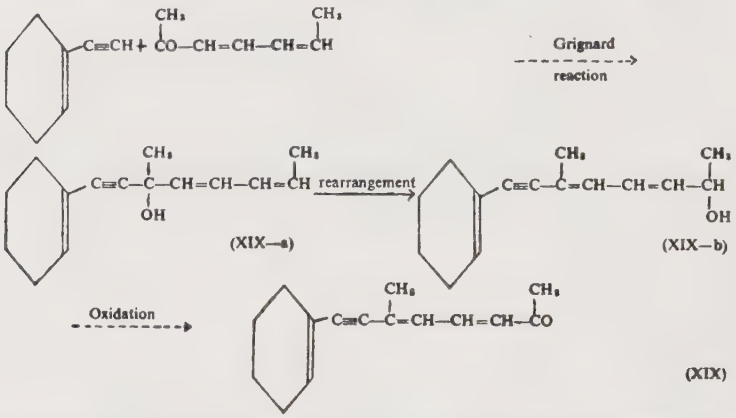
(XVII)



(XVIII)

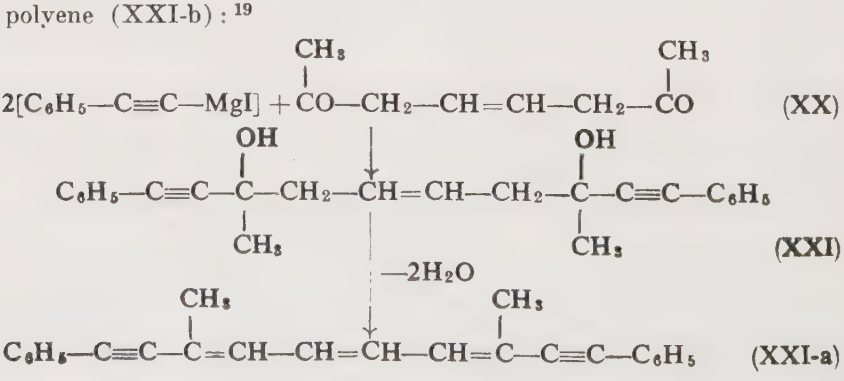
(e) Crotonylideneacetone can be condensed with ethynylcyclohexene[17] through the Grignard reaction to give the carbinol (XIX-a)

which after anionotropic rearrangement to the isomeric secondary carbinol (XIX-b) can be oxidised to (XIX). Through the Reformatsky condensation of (XIX) with methyl bromoacetate a crystalline C_{17}-acid analogous to the vitamin A acid can be obtained.

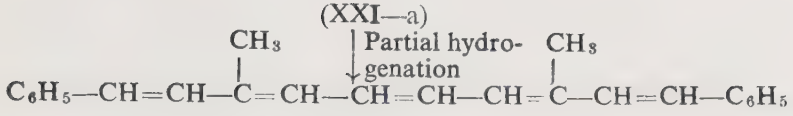


(f) Karrer and co-workers have been employing propargyl magnesium bromide and octen-4-dion-2,7 in the syntheses of various polyene pigments. This forms one of the main methods by which the carbon skeleton can be lengthened :

1. Karrer and Eugster condensed phenylacetylene magnesium iodide with octen-4-dion-2,7 (XX) and obtained carbinol (XXI). Elimination of water molecules from (XXI) yielded compound (XXI-a) which on partial hydrogenation was converted into the polyene (XXI-b) : [19]

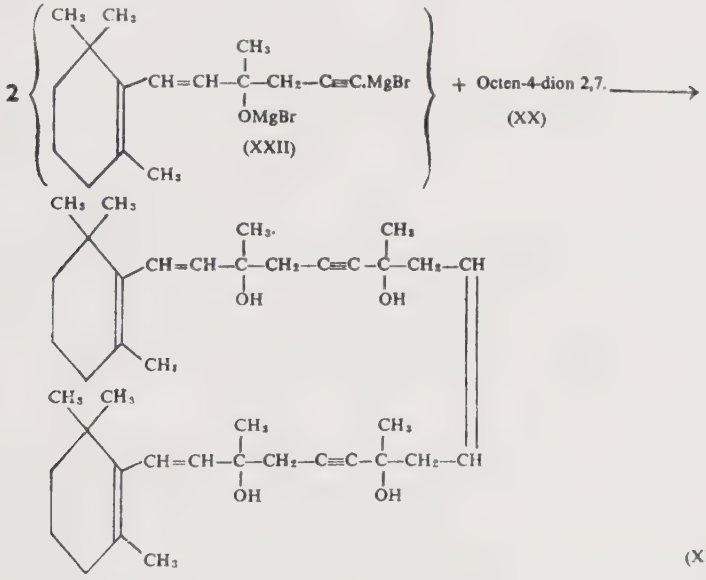


(XXI—a)



(XXI-b)

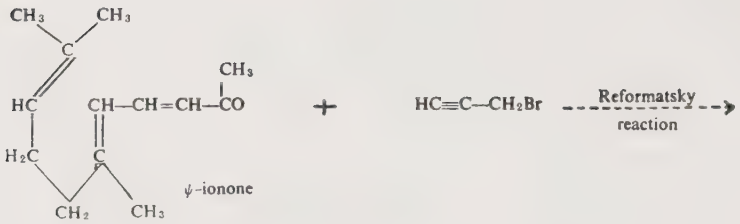
2. By the Grignard condensation of compound (XXII) with compound (XX), Karrer and Eugster[20] obtained the tetrol (XXIII) which on partial hydrogenation with palladium and hydrogen and subsequent dehydration yielded β-Carotene.

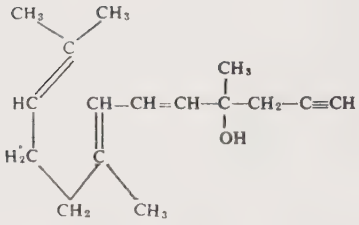


(XXIII)

3. In a similar way,[21] the condensation product of propargyl bromide and α-ionone has been reacted with octen-4-dion-2,7 (XX) to obtain a highly unsaturated tetrol, an intermediate product in the synthesis of ε_1-carotene.

4. Synthesis of lycopene by Karrer et al[22] : By the Reformatsky condensation of ψ-ionone with propargyl bromide, acetylenic carbinol (XXIV) was obtained which on Grignard condensation with octen-4-dion-2,7 (XX) yielded the corresponding tetrol. This tetrol on partial hydrogenation and dehydration yielded lycopene:





.....(XXIV)

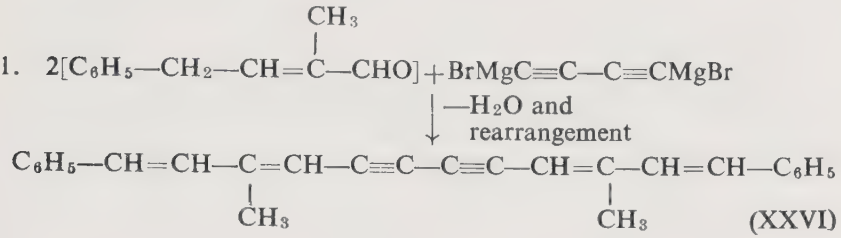
5. The acetylenic carbinol (XXV) can be obtained[23] by condensing propargyl bromide with benzalacetone. Its dimagnesium salt can be coupled with octen-4-dion-2,7 to get the corresponding tetrol, from which a mixture of coloured pigments can be obtained on dehydration and partial hydrogenation:

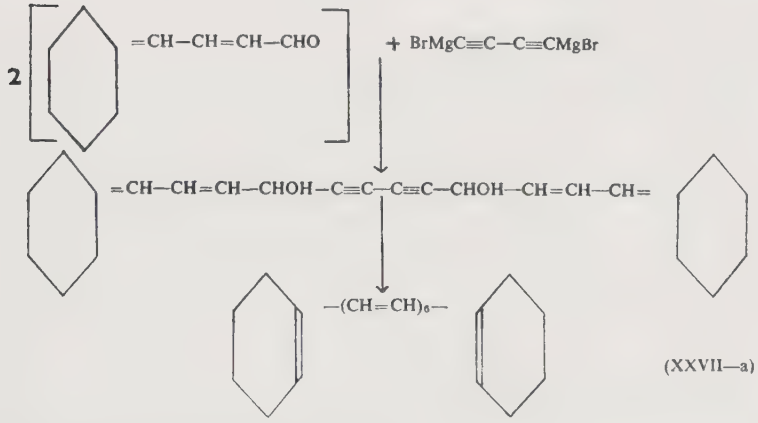
$$C_6H_5—CH=CH—\underset{\displaystyle OH}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}—CH_2—C\equiv CH \qquad \text{(XXV)}$$

6. Quite recently γ-carotene has been synthesised by Karrer et al[24]. By the Grignard condensation of compounds (XXIV) and (XXII) with octen-4-dion-2,7 (XX), they obtained a mixture of tetrols which on partial hydrogenation and dehydration yielded a mixture of γ-carotene and β-carotene along with a small quantity of lycopene:

(XXIV) + (XX) + (XXIV) ⟶ Lycopenne
(XXIV) + (XX) + (XXII) ⟶ γ-Carotene
(XXII) + (XX) + (XXII) ⟶ β-Carotene

(g) Diacetylene, in the form of its magnesium bromide, is very useful in synthesising compounds with several C = C groups in conjugation with acetylenic linkages.[25]





PROPERTIES AND APPLICATIONS:

In general, these polyacetylene compounds undergo rearrangement and partial hydrogenation. When it is a carbinol, elimination of water can be effected to obtain compounds with several— C = C — groups in it. These properties have found various applications in different syntheses.

Hydrogenation:

Polyacetylenes can be hydrogenated completely to give the corresponding saturated hydrocarbons. For example, mycomycin[7] requires eight moles of hydrogen, yielding quantitatively n-tridecanoic acid.

On partial hydrogenation, usually palladium is used as the catalyst, the triple bonds are reduced to double bonds. During this process, isomerisations are not likely to occur. Hence this method has distinct advantages over many others for the syntheses of ethylenic compounds containing the — CH = CH — grouping. Also, the partial hydrogenation of an isolated acetylenic linkage is stereo-selective, giving rise mainly to the cis-configuration of the resulting ethylenic bond.[1] Examples of hydrogenation are found in: β-carotene, γ-carotene, vitamin A and a host of others.

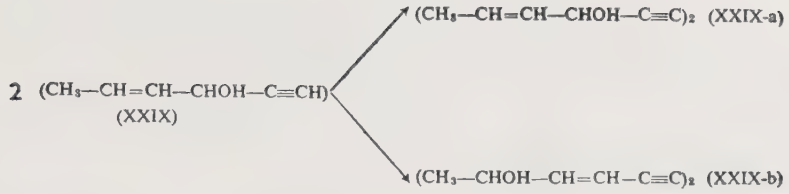
Anionotropic Rearrangement:

The acetylenic carbinols and glycols undergo an unusual rearrangement.[26]. Burton and Ingold[27] made a systematic study of this rearrangement. They mention that the ease of isomerisation in such a system would be expected to increase with increasing strength of the acid HX, where X is the migrating anion —Br > OAc > OH. Vinylethynyl carbinol and styrylethynyl carbinols however do not isomerise even at high concentration and temparature.[26]

The rate of anionotropic rearrangement is variable. In some cases, as in propenylethynyl carbinol, it is accelerated by increase of temperature and also by increase in concentration of the acid.[28] In many cases, 5% acid is sufficient to effect the rearrangement.

(a) $CH_3CH{=}CH{-}CHOH{-}C{\equiv}CH \xrightarrow[\text{quantitative}]{5\%\ \text{acid}} CH_3{-}CHOH{-}CH{=}CH{-}C{\equiv}CH$ (XXVIII)

(b) In oxidative coupling, the control over the acidity is very essential.[29] In this way, it is possible either to get the glycol (XXIX-a) or the corresponding rearranged glycol (XXIX-b) from (XXIX):



(c) Treatment of an ethereal solution of the acetylenic glycol with 10% sulphuric acid brings about a dual anionotropic rearrangement resulting in the formation of the isomeric glycol :

$$CH_3—CH=CH—CHOH—C\equiv C—CHOH—CH=CH—CH_3$$
$$\downarrow \text{ 10\% acid}$$
$$CH_3—CHOH—CH=CH—C\equiv C—CH=CH—CHOH—CH_3 \text{ (XXX)}$$

(d) But dec-2-en-5-yn-4-ol (XXX-a) does not isomerise when shaken with 10% acid for twenty-four hours. 25% acid is needed for its rearrangement to dec-3-en-5-yn-2-ol (XXX-b). The yield is quantitative.[26]

$$CH_3—CH=CH—CHOH—C\equiv C—CH_2—CH_2—CH_2—CH_3 \text{ (XXX-a)}$$
$$\downarrow \text{ 25\% acid}$$
$$CH_3—CHOH—CH=CH—C\equiv C—CH_2—CH_2—CH_2—CH_3 \text{ (XXX-b)}$$

(e) In the case of mycomycin[7], isomerisation to isomycomycin takes place in normal aqueous potassium hydroxide at 27° involving an allene to acetylene isomerisation accompanied by migration of the existing acetylenic bonds: Compound IV $\xrightarrow{27^\circ}$ V.

Dehydration :

Carbinols with acetylenic and ethylenic bonds can be dehydrated with toluene-p-sulphonic acid. For example, Compound XXI, on removal of two moles of water, yields compound XXI-a. The tetrol XXIII, on removal of four moles of water and partial hydrogenation, yields β-carotene (pages 10 and 11).

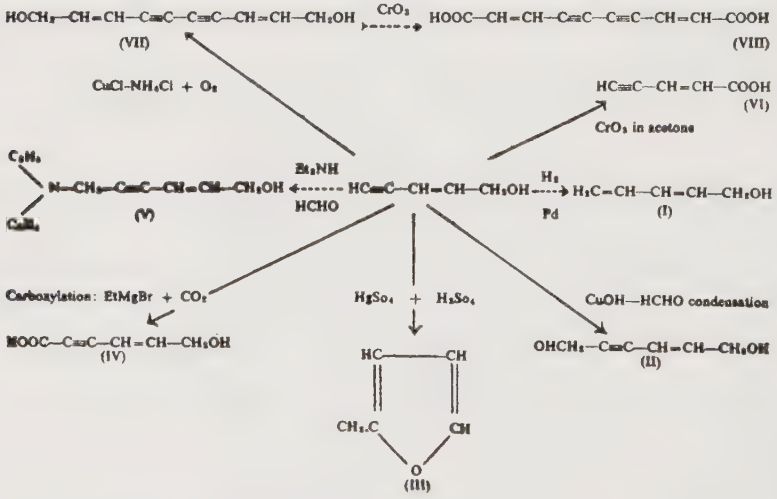
These three properties have found wide application in various syntheses like vitamin A, its analogues, and various carotene pigments.

Reactions with Diazomethane :

Unsaturated acids like mycomycin, matricaria acid and nemotinic acid react with diazomethane to form methyl esters which, in some cases, are more stable. On using a great excess of diazomethane, the acetylenic group may enter into the reaction forming a pyrazole derivative. (See experimental part, page 32.)

Reactions of ethynyl ethylenic alcohols have been discussed in this and the next page.

Properties :



Reactions of ethynyl ethylenic alcohol : [26]

I. Partial hydrogenation.

II. Condensation with HCHO.

III. Hydration with $HgSO_4$ and H_2SO_4 ——————→
Methyl furan (yield : 35%)

IV. Carboxylation of ethynyl carbinols is done by careful attention to the reaction conditions, especially to the choice of solvent for the Grignard complex, excellent conversions into the hydroxy acetylenic acids being obtained.[34]

V. Mannich condensation.

VI. Simple oxidation reaction with CrO_3.

VII. Oxidative coupling.

ABSORPTION SPECTROSCOPY :

In the isolation and characterisation of many unsaturated compounds, light absorption data in the wavelength range of 2000--10,000 Å has found wide application. Conjugation has a particularly large effect on ultraviolet-absorption properties, resulting in the appearance of new bonds which are characteristic of the conjugated system. They are invariably situated at longer wavelengths than those with the isolated chromophores. Combinations of the two conjugated chromophores usually exhibit similar high intensity bands in the 2000-2300 Å region.[30]

		Maxima Å
Butadiene	... C=C—C=C ...	2170
Vinylacetylene	... C=C—C≡C ...	2190

In more extended conjugated systems, the characteristic bands are progressively displaced towards longer wavelengths. When the number of conjugated chromophores reaches between six and nine, the K bands fall in the visible region and intense colour results :

n=3	C=C—C≡C—C=C	divinylacetylene	2550 Å	colourless
n=5	$(C=C)_5$	vitamin A	3280 „	pale-yellow
n=11	$(C=C)_{11}$	lycopene	4720 „	red

The conjugated vinylacetylene system somewhat resembles a conjugated diene system in light absorption properties, though the intensities of the former are lower than those of typical dienes. The triple bond is rather akin to the carbonyl bond which when conjugated to an ethylenic linkage, gives rise to a maximum in the 2200–2500 Å region. They show a marked inflexion at 2300 Å. Complete substitution in the acetylenic group has little or no effect on the location and intensity of the maximum and the inflexion is apparent. The intensity of the absorption of the conjugated dienyne system is much less than that of the conjugated trienol.[16]

	max Å	ε max	max Å
Deca-3:7-dien-5-yn-2:9-diol	....	....	2650
Its acetate	2560	14,000	2650
7-methylnona-3:7-dien-5-yn-2-ol	....	....	2640
Octatrienol	2560	42,500	2645

The conjugated diacetylene chromophore exhibits absorption at rather longer wavelengths than the conjugated vinylacetylenes and dienes. But the intensities are only of low order. There is a progressive diminution in the intensity accompanied by appearance of fine structure in the conjugated diene, en-yne, and di-yne systems.

"The conjugated diacetylene glycols show complex absorption of low and very variable intensity in the 2200–3000 Å region with important differences between compounds of very similar structures. With pure compounds, the light absorption properties of diacetylenes are quite regular and their absorption does not extend with appreciable intensity beyond about 2650 Å. The light absorption of these compounds is approximately constant over a small range of substituents and permits the deduction that the substitution of alkyl for hydrogen in monosubstituted diacetylenes has only a small effect. The average bathochromic shift is 20 Å for the longest wavelength band as against 50 Å for alkyl substitution in dienes."

— E. R. H. Jones et al.[29]

APPLICATION OF ABSORPTION SPECTROSCOPY TO ORGANIC COMPOUNDS :

1. Qualitative analysis : Identification of compounds, investigating the structural details.
2. Quantitative analysis : Determination of concentration and purity.
3. Physico-chemical : Molecular constants, reaction-rates, absorption phenomenon.

Castille[31] proposed the formula (XXXI) for erythrogenic acid. But the comparison[29] of the absorption spectra of this with those of typical vinylacetylenes[26] and with the diacetylene spectra recorded[29] eliminates formula (XXXI) and suggests that erythrogenic acid is a mixture of compound (XXXII) with 6% of a C_{18}-acid having a —C=C—C≡C—C≡C— chromophore.

$CH_2=CH—C\equiv C—(CH_2)_4—C\equiv C—(CH_2)_7—COOH$ (XXXI)

$CH_2=CH—(CH_2)_4—C\equiv C—C\equiv C—(CH_2)_7—COOH$ (XXXII)

	max Å	max Å	max Å	max Å
Erythrogenic acid	2275	2400	2530	2666
Propenyldiacetylene	2300	2380	2510	2640

It has been observed that compounds containing conjugated polyacetylenic linkages have well defined absorption with long wavelength maxima spacings between 1900–2300 cm^{-1} corresponding to acetylenic vibrational frequencies. Infra-red bands near 1580 and 1620 cm^{-1} have been associated with C = C stretching absorption.[32]

Example :

Mycomycin in dioxane exhibits characteristic bands near :

3180cm^{-1} attributed to ≡CH function
2210cm^{-1} „ „ disubstituted—C≡C—[33]
1930cm^{-1} „ „ —CH=C=CH— and
1730cm^{-1} „ „ unconjugated—COOH functions.

Ultraviolet spectra:[2]

cis-Lachnophyllum ester	224.0	inflex	277.0	291.1	308.8	in hexane
trans ester	223.5	256.8	271.0	287.2	305.3	in hexane
compound from clitocybe diatreta (–C≡C–C≡C–C=C–COOR)	225.0	260.0	275.0	291.0	310.0	in ethanol
cis-Dihydromatricaria acid	215.0	239.0	251.5	265.5 (in hexane)		
$CH_2=CH—C\equiv C—C\equiv CH$		236.0	248.0	262.0 (95% ethanol)		
$CH_3—CH=CH—C\equiv C—C\equiv CH$		238.0	251.0	264.0 (95% ethanol)		
Nemotin (—C=C—C≡C—C≡C)	207.0	236.0	248.0	262.0 (in water.)		

Experimental

PART I

EXTRACTION WORK :

A few carotenoid pigments were isolated from plant extracts. Here below is the summary of the paper[44] published in the *Helv. chim. Acta Volume XXXIV, 1951, page 2159.*

Occurrence of Capsorubin :

Till now, capsorubin has been found only in the fruits of Capsicum annum together with capsanthin.[35] The rarity of its occurrence justifies this reference about the presence of the pigment in the fruits on Encephalartos Villosus.

The benzene or acetone extract of the above-mentioned fruits was saponified with alcoholic potassium hydroxide as usual, separating the coloured pigments into hypophasic and epiphasic parts. The hypophase was chromotographed on zinc carbonate, developing with benzene. The upper layer, after rechromotographing twice, yielded 40 mg. of a pigment which crystallised from carbon disulphide. The properties of this pigment were very similar to those of capsorubin. It had a melting point of 200°.

Absorption maxima in :

Carbon disulphide	541.5mμ	503mμ
Benzene	524.0mμ	486mμ
Hexane	502.0mμ	470mμ

Analysis: $C_{40}H_{60}O_4$	Calculated :	C=79.41%	H=9.97%
	Found :	C=78.83%	H=9.63%

Probably the fruits of Encephalartos Villosus contain besides zeaxanthin, β-carotene and α-carotene, minor quantities of lycopene or γ-carotene. These pigments were not however isolated in the cry-

stalline state. But it was possible to establish their presence through absorption spectrum analyses. The presence of capsanthin in Encephalartos Longifolium has been proved both by mixed chromotography and by spectrum analysis. Probably zeaxanthin is also present. We thank Dr. Enslin, Pretoria, for having provided with the plant material.

PART II

SYNTHETIC WORK :

In the following two syntheses, propargyl bromide has been condensed with adipaldehyde and oxalic acid monoethylester chloride through the Grignard reaction. In the former case, the condensation product was obtained in the crystalline form, but it was not analytically pure. The second reaction yielded dipropargylglycolic acid. Various derivatives were made of the above mentioned substances in order to confirm their structure.

In all the following reactions, pure and dry solvents were used. Apparatus used was made moisture free.

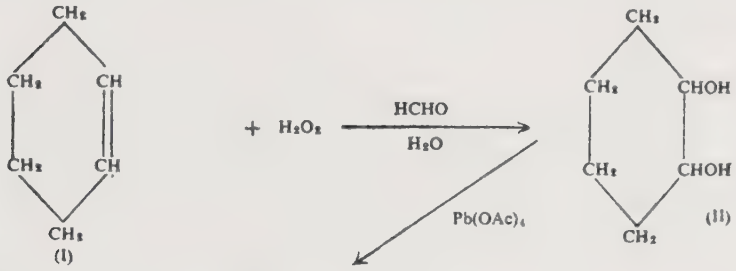
SYNTHETIC PART A :

Condensation reaction of propargyl bromide with adipaldehyde :

Trans-cyclohexane-diol-1,2 (II)[36] prepared from cyclohexene (I) was oxidised with lead tetraacetate[37] to obtain adipaldehyde (III).[38] The diacetylenic carbinol (IV) was obtained by the Grignard condensation of (III) with propargyl bromide.[39] The aim of this synthesis was to obtain compound (V) by dehydration of (IV) and converting (V) into its acid compound (VI).[40]

Compound (IV) melted between 68·5° — 69°, but on sublimation, the melting point was lowered. M.P : 66° — 68°. Purification through chromotography was tried but with no success. The different analyses made of the substance gave varying values.

Purification of compound (IV) through its silver salt did not improve the analytical value of the acetylenic carbinol (IV). Tests with Girard's Reagents and dinitrophenylhydrazine were negative indicating the absence of carbonyl groups. Acetylation was carried out with acetic anhydride and the oil so obtained was not analytically pure. The oil was hydrolysed and compound (IV) was obtained. Analysis showed that it was still impure. On hydrogenation, the compound (IV) used up four moles of hydrogen, as expected.



$$OHC-(CH_2)_4-CHO \qquad \text{(III)}$$

$$\downarrow \; Mg + HC{\equiv}C-CH_2Br$$

$$HC{\equiv}C-CH_2-CH(OH)-(CH_2)_4-CH(OH)-CH_2-C{\equiv}CH \qquad \text{(IV)}$$

$$\downarrow \; -2H_2O$$

$$HC{\equiv}C-HC{=}CH-(CH_2)_4-CH{=}CH-C{\equiv}CH \qquad \text{(V)}$$

$$\downarrow \; \text{carboxylation}$$

$$HOOC-C{\equiv}C-HC{=}CH-(CH_2)_4-CH{=}CH-C{\equiv}C-COOH \qquad \text{(VI)}$$

Reformatsky Reaction :

Activated zinc wool (17gm) was taken in a two-necked flask fitted with a condenser and a dropping funnel. Tetrahydrofuran (200cc) was added to cover the solid in the flask. Propargyl bromide (24·8gm) was mixed with freshly distilled adipaldehyde (10gm) in the dropping funnel. One-third of the mixture was run into the

flask at one stretch, a crystal of iodine was added and the flask warmed. The reaction was slow and not vigorous. Propargyl bromide-adipaldehyde mixture was added dropwise during one hour, after which the reaction mixture was refluxed for forty-five minutes, cooled and hydrolysed with 250cc 2N sulphuric acid and 350gm of powdered ice. The reaction product was extracted several times with ether, the ether extract was washed free of acid, then with ammonium sulphate solution followed by water. The ether layer was dried over anhydrous sodium sulphate and evaporated under vacuum. A reddish oil (8gm) was obtained.

The reddish oil was at first distilled in a kugelrohr at 100°/12mm pressure to remove the unreacted aldehyde and then at 130°/10mm. A light yellow liquid, giving a negative test with alcoholic silver nitrate reagent showing the absence of $\equiv$CH grouping, was obtained. Its analysis was as follows :

C : 76.12% and H : 8.74%.

This distillate was discarded. The residue, which was about a gram and half, was distilled under high vacuum. Two fractions were collected :

			reaction with alc. $AgNO_3$
I.	460mg viscous yellow oil . . .	100-105°/0.02mm distilled twice	$\equiv$CH group present
II.	450mg pale yellow viscous liquid . . .	130-140°/0.05mm distilled twice	$\equiv$CH group present

Found :

Fraction I . C : 73.47% H : 9.29%
Fraction II. C : 72.13% H : 9.43%

Calculated C : 74.23% H : 9.28% (Compound IV—$C_{12}H_{18}O_2$)
,, C : 70.12% H : 9.01% (Mono compound—$C_9H_{14}O_2$)

A modification in the above condensation reaction was made and with greater success. The Grignard reaction was found to be suitable.

Grignard reaction :

Activation of magnesium : Magnesium turnings (7gm) were treated with 100cc of 1% mercury chloride solution for about half a minute. The solution was decanted, the darkened magnesium turnings well washed, rinsed with alcohol and then with ether, and the compound dried at 80° over phosphorus pentoxide and calcium chloride under vacuum for one hour.

Propargyl magnesium bromide was prepared as follows : Activated magnesium (7gm) mixed with ether (250cc) was taken in a one-litre three-necked flask fitted with a dropping funnel, reflux condenser and stirrer. Propargyl bromide (32gm) diluted with ether (70cc) was taken in the dropping funnel. One-third of this mixture was run into the flask and the flask was warmed slightly. In less than twenty minutes the reaction had started and the propargyl bromide-ether mixture was added in drops to the activated magnesium during one and half hours. After the addition was complete, the mixture was refluxed for one hour more and cooled. Yield : 80%.

Grignard condensation: Freshly distilled adipaldehyde (11.4 gm) diluted with ether (200cc) was dropped to propargyl magnesium bromide during two hours, with vigorous stirring. After the addition of all the adipaldehyde, the reaction mixture, which was a pale-brown sticky mass, was refluxed for one hour and left overnight at room temperature.

Hydrolysis and extraction : The next day, the reaction product was hydrolysed with well-cooled 2N sulphuric acid, (ammonium chloride was tried at first, but large quantities were needed) the aqueous layer was saturated with common salt, and extracted with ether several times. The ether layer was washed with bicarbonate fol-

lowed by water saturated with salt, dried over anhydrous sodium sulphate and evaporated under vacuum. A dark-red viscous liquid (13gm) was left behind, which was distilled in a kragenkolben under high vacuum.

4gm	light yellow oil	80°/0.02mm
6gm	yellowish-green oil which decomposed partly	108°/0.02mm

The above Grignard reaction was repeated in order to obtain enough starting material for further work. After repeated distillations, a yellowish oil (12gm) distilling between 110–130°/0.02mm was collected.

Crystallisation : The yellow oil (12gm) was dissolved in acetone (20cc) and cooled to —60° for one hour. The crystals which separated slowly, were quickly filtered under suction at —40° and dried over calcium chloride in vacuum. A white crystalline substance (5·6gm) melting between 53 — 59° was obtained, which on recrystallisation from acetone, yielded a compound (4·42gm) melting between 60—64° .. .. (Product P-1)

The mother liquor was refluxed with a mixture of methanol (60gm), Girard's P Reagent (5gm) and glacial acetic acid (6gm) for one hour and cooled. The product was added to water (50cc) + ice powder (50gm)+2N sodium hydroxide (45cc being 9/10 of the calculated quantity required to neutralise the acid), and the reaction product extracted with ether several times, the ether layer washed, dried and evaporated as usual. The residue was distilled under high vacuum :

Fraction I.	Few drops of a pale-yellow liquid	90°/0.01 mm
.. II.	3.4gm yellow oil 10-120°/0.01 mm	.. (P-2)

Analysis of P-2 : Found : C : 70.25%
H : 9.04%

Enough acid was added to the aqueous layer to make the solution 1N. After one hour, the solution was extracted with ether and the ether extract evaporated. There was no residue indicating the absence of a carbonyl group in the product P-2.

Product P-1 (3.42gm) was dissolved in warm benzene (40cc) and warm petrol ether was added to it and the mixture allowed to cool slowly. Flaky crystals separated (2.5gm).

Melting point=68.5—69° .. .. (P-3)

Reactions with P-1 and P-3 :

(a) *Girard's P Reagent*: P-1 (700mg) was refluxed for one hour with an equal quantity of Girard's P Reagent+glacial acetic acid (0.1cc) + methanol (7cc). The reaction product was cooled and extracted with ether and the ether layer worked up in the usual manner.

700mg Yellow viscous oil 110°/0.015mm Found : C : 71.55%
H : 9.16%

The oil was crystallised from benzene-petrol ether mixture and the crystals were sublimed under vacuum :

Fraction I. 90°/0.02mm M.P.: 63-67° Found: C: 69.69%
H: 8.26%

Fraction II. 100°/0.02mm M.P.: 62-68° Found: C: 72.43%
H: 9.24%

Calculated for compound IV — $C_{12}H_{18}O_2$ C: 74.23%
H: 9.29%

(b) *Girard's T Reagent* : This reaction was conducted by refluxing product P-1 (350mg) with Girard's T Reagent (400mg) + glacial acetic acid (0.1cc) + methanol (4.5cc). The crystalline residue obtained after working up the reaction product was sublimed slowly during eight hours:

Fraction I. 80°/0.02mm M.P.: 66°-68° Found : C: 73.21%
H: 8.79%

Fraction II. 100°/0.02mm M.P.: 67° Found : C: 72.73%
H: 8.79%

(c) 2,4-*dinitrophenylhydrazine* was refluxed with P-3 (25 mg) in methanol for one hour. Neither crystals nor precipitate of dinitrophenylhydrazone was observed.

The negative results obtained from the above reactions suggested the absence of carbonyl group in products P-1, P-2 and P-3.

(d) *Microhydrogenation* : Product P-3 (4.06mg) was hydrogenated using platinum catalyst in glacial acetic acid (5cc) at 20°/723mm. The hydrogenation was complete in 20 minutes, using 2.031cc of hydrogen. ($V_0 = 1.855$) 3. 956moles

The hydrogenation was repeated using 5.549mg of P-3 at 19.5°/722mm. The reaction was complete in 20 minutes. Hydrogen used up was 2.920cc. ($V_0 = 2.585$) 4. 060moles

On the average, P-3 used up for hydrogenation 4. 008moles

Calculated for compound IV ($C_{12}H_{18}O_2$) 4. 000moles

(e) *Silver salt* : It is known that —C≡CH groups react with silver nitrate to give a silver complex :

$$—C{\equiv}CH + AgNO_3 \longrightarrow$$
$$—C{\equiv}C—Ag + AgNO_3 \longrightarrow$$
$$—C{\equiv}C—Ag_2NO_3$$

Excess of alcoholic silver nitrate (650mg in 5cc of 5% alcohol) was added in drops with shaking to P-1 (500mg) dissolved in alcohol (10cc) and the heavy precipitate was filtered. To the clear filtrate more alcoholic silver nitrate solution was added till there was no more precipitation and filtered. Both the precipitates were taken together and warmed with alcohol (50cc) for an hour and decanted. (The filtrate on evaporation, left no residue.) The heavy solid was

carefully powdered, shaken with a mixture of hydrochloric acid (40cc, 1%) and ether (50cc) for two hours and left overnight at room temperature. The next day the acid layer was extracted with ether several times and the combined ether extract was washed well with water, dried and evaporated as usual. The residual oil was crystallised from ether-petrol ether mixture.

170mg	M.P. : 69.8°	Found :	C : 71.20% H : 7.86%
		Calculated for compound IV-$C_{12}H_{18}O_2$	C : 74.23% H : 9.29%
The above crystals were sublimed under high vacuum.		Found :	C : 72.76% H : 8.84%

70mg of substance with the same melting point as above, viz., 69.8° were recovered from the mother liquor.

(f) *Chromotography* : P-1 (200mg) was dissolved in benzene (10 cc) and ether (3cc) and chromotographed on alumina of grade 1-2, eluting with varying quantities of benzene + ether; ether; ether + methanol; and methanol. Twenty fractions were collected.

Size of column : 14 x 1.8cm

Fractions : 10	... 7.3mg	crystallised from ether + petrol ether mixture and sublimed, M.P. : 66-68°	
+			
11	... 14.0mg	on recrystallisation, M.P. : 68.6-69°	
12	... 2.5mg	crystallised as above, M.P. : 68.5-69°	
+			
13	... 156.0mg	M.P. on sublimation : 66-68°	
		Analysis of the sublimate.	
14	... 18.9mg	Found : C : 73.53%	
	198.7mg	H : 9.23%	
		active H : 0.99%	cold
		„ H : 1.56%	warm
		Calculated for Compound IV active C : 74.23% H : 9.29% H : 2.00%	$C_{12}H_{18}O_2$

Product P-1 was chromotographed several times, but with little success. The substance was not obtained in the analytically pure state.

(g) *Acetylation* : An acetyl derivative of compound IV was made by adding acetic anhydride (300mg) in drops to a well cooled solution of P-3 (300mg) in freshly distilled pyridine (3cc) with shaking. The reaction mixture was hydrolysed after fifteen hours, extracted with ether and the ether layer worked up as usual. The residue so obtained was distilled under high vacuum:

250mg colourless liquid 100°/0.01mm Found : C: 68.44% H: 7.99%

Calculated for compound $C_{16}H_{22}O_4$: C: 69.06% H: 7.91%

The acetyl derivative was decomposed with alkali and the starting material, compound IV (P-3), was recovered and crystallised.

M.P: 68.5–69°. P-3 gave different values on analysis:

C: 73.02% ... 74.16% ... 70.71% ... 72.57%

H: 8.65% ... 9.54% ... 8.26% ... 9.01%

Calculated for compound IV — $C_{12}H_{18}O_2$ C: 74.23% H: 9.29%

Reaction with Diazomethane :

P-3 (100mg) was kept in contact with an ethereal solution of diazomethane for a week. After working up the reaction product, only the starting material, P-3 was obtained. The acetylenic bonds of compound IV did not react with diazomethane to give pyrazole derivatives.

Reactions with the oily product, P-2 :

(a) P-2 was converted into its silver compound with silver nitrate. The precipitate was decomposed but only an oil was obtained. No crystals could be obtained from it.

(b) The acetyl derivative of P-2 was made and on subsequent decomposition with alkali, only an oil was obtained. It could not be crystallised. Also, its analyses gave inconsistent and incorrect values.

SYNTHETIC PART B:

Synthesis of Dipropargylglycolic Acid (Compound III)

Oxalic acid monoethylester chloride (II) was reacted with propargyl magnesium bromide at —60° employing a great excess of (II). Along with dipropargylglycolic acid (III) a large quantity of oxalic acid was also formed. The former could be freed from the by-product oxalic acid by initial extraction with ether followed by benzene.

$$C_2H_5—O—CO—COOK \qquad \text{(I)}$$

$$\downarrow + SOCl_2$$

$$C_2H_5—O—CO—CO—Cl \qquad \text{(II)}$$

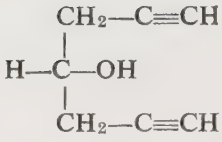
$$\downarrow + 2HC{\equiv}C—CH_2MgBr$$

$$\begin{array}{l} \quad CH_2C{\equiv}CH \\ \quad\quad | \\ HOOC—C—OH \\ \quad\quad | \\ \quad CH_2C{\equiv}CH \end{array} \qquad \text{(III)}$$

Acid III gave a bulky precipitate with alcoholic silver nitrate confirming the presence of terminal≡CH grouping. On hydrogenation, acid III took four moles of hydrogen yielding dipropylglycolic acid (IV).

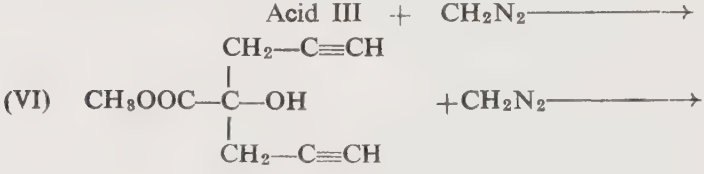
$$\begin{array}{l} \quad CH_2\ CH_2\ CH_3 \\ \quad\quad | \\ HOOC—C—OH \\ \quad\quad | \\ \quad CH_2\ CH_2\ CH_3 \end{array} \qquad \text{(IV)}$$

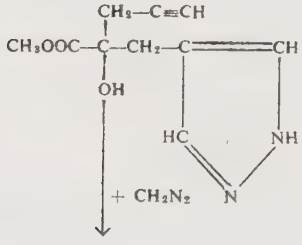
Attempts to obtain compound (V) by distilling (III) with sodamide did not prove successful.



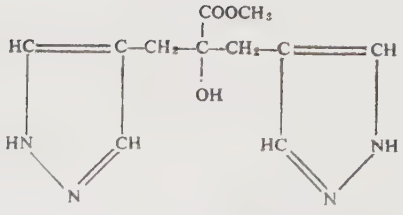
(V)

It is known that acetylene compounds react with diazomethane to give pyrazole derivatives. Acid (III) can react with diazomethane in three ways to give: (a) the methyl ester (VI), (b) the mono-pyrazole derivative (VII) where only one ≡CH group enters into reaction and (c) the di-pyrazole derivative (VIII) where both the ≡CH groups react with diazomethane. In our hands, the reaction yielded only compounds VI and VII.





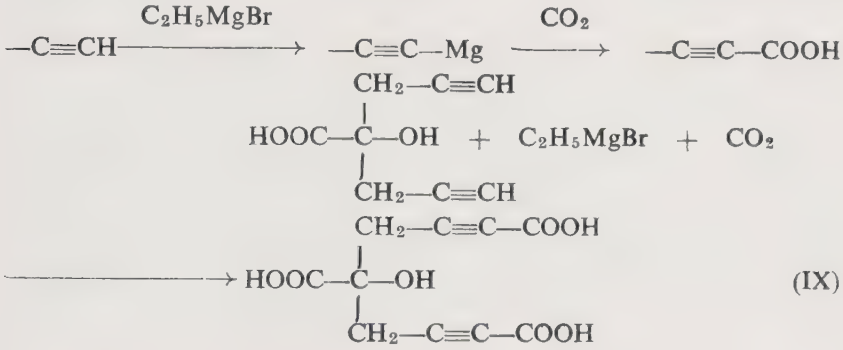
(VII)



(VIII)

Carboxylation of acetylenic compounds like R—C≡C.CH_2Br[42] and —C≡CH groups[40] have been realised by treating the Grignard complex of the compound with dry ice and ether in an autoclave.

The choice of the solvent has been found to be necessary since the solubility of the initial Grignard complexes has considerable influence upon the yield of the acid. Normally the yields obtained were 70–80%. In an analogous manner, compound (IX) should be derivable from (III). However the reaction did not go.



(IX)

Oxalic acid monoethylester chloride[41], compound (II), was prepared as follows: Freshly distilled thionyl chloride (80gm) was added dropwise to monoethylester of potassium oxalate (compound I, 50 gm) the reaction mixture being cooled to 0°. After the addition was complete, the reaction product was allowed to attain room temperature, heated on a water-bath for fifteen hours, cooled and filtered on a Buchner funnel, washed with ether and distilled. The fraction distilling between 125–138° was collected. (60% yield)

Propargyl bromide[39] was prepared by adding propargyl alcohol to well-cooled phosphorus tribromide.

Grignard Reaction :

Propargyl bromide (48gm) dissolved in ether (200cc) was converted into its Grignard complex by reacting it with activated magnesium turnings (11.5gm) in ether (200cc). Propargyl magnesium bromide was added in drops during half an hour with stirring to

oxalic acid monoester chloride (II) in ether (250cc). The contents of the flask were cooled to —20°. The reaction mixture turned brown. After fourteen hours, it was refluxed for half an hour, cooled and hydrolysed with acetic acid and extracted several times with ether as usual. After working up the ether layer, an oily residue (30gm) was obtained .. .. Substance *S*-1.

Conversion of S-1 into its sodium salt:

2N sodium hydroxide (220cc) was added in drops to well-cooled S-1 (30gm) dissolved in a mixture of alcohol (200cc) and water (200cc). After allowing to stand for three hours at room temperature, more water was added to the reaction product to dissolve the sodium salt and then filtered. The filtrate was extracted several times with ether, and the neutral ether layer discarded.

Regeneration:

The aqueous layer was cooled with ice-salt mixture, acidified with 2N hydrochloric acid (230cc), saturated with salt and extracted several times with ether. After working up the ether extract in the usual way, a dark-brown oily residue was obtained which could not be crystallised. Attempts to purify the oil by chromotography on alumina were not helpful. Therefore, the oil was extracted a few times with hot water and the aqueous extract evaporated under vacuum. The residue so obtained yielded on distillation at 100°/0.015mm, pale-yellow crystals, (1.12gm) melting between 70°-93°. They were sublimed under high vacuum at 100° to give one gram of substance (S-2) with M.P: 85-93° *S*-2

The whole reaction was repeated with a few variations. Propargyl bromide (65gm) was reacted with activated magnesium (14gm) in the usual way. A solution of the Grignard compound so obtained was added in drops during two hours to II (75gm in 500cc ether) with stirring. The reaction was conducted at —60°, the Grig-

nard complex decomposed after twelve hours and worked up as usual A dark-brown oil (60gm) was obtained. *S*-3

Ether was added to the oil S-3, when a precipitate was obtained. This was filtered and the precipitate discarded. The filtrate was evaporated in vacuo and the residue distilled in ten portions. A yellow oil (47gm) was obtained at 120°/10mm. ..... *S*-4.

The yellow oil S-4 was converted into its sodium salt and filtered. Only a part of the sodium salt of S-4 went into solution while the rest (58gm, S-5) was collected on the filter. .. .. *S*-5.

The filtrate was extracted with ether, and the neutral ether layer was discarded. The aqueous layer was neutralised with acid and extracted with ether. Removal of the solvent from the ether extract yielded a yellow oil .. .. *S*-6.

The sodium salt S-5 (58gm) was decomposed with large quantities of dilute acid and the aqueous layer worked up as usual. We obtained a yellow residue. .. .. *S*-7.

S-6 and S-7 were crystallised from benzene-ligroin mixture. The dark-brown crystals thus obtained (3.4gm, M.P: 70–90°) were distilled under high vacuum (80–90°/0.02mm) in five portions to yield 2.6gm of a yellow powder of M.P: 90–100°. This powder on sublimation at 70°/0.02mm, yielded the pure compound (III) melting at 103°.

Analysis of the compound with M.P: 103°.

Found :	C: 62.88%	Calculated for	C: 63.16%
	H: 5.93%	III ($C_8H_8O_3$) :	H: 5.26%

The water layer of the acidified S-5 contained still some acid (III) along with oxalic acid. The mixture was extracted with ether and the solvent removed. The crystalline residue was refluxed with warm benzene and filtered. Oxalic acid (6gm) was collected on the

filter. The filtrate contained 200mg of acid III which was recovered by evaporating the solvent.

Dipropargylglycolic acid (III) is very hygroscopic, soluble in water, ether, and acetone, but sparingly soluble in benzene. The acid can be crystallised from chloroform or benzene. The impure crystals are yellow, sticky and have an unpleasant smell.

Reactions with Dipropargylglycolic Acid:

1. *With sodamide.* Acid III (100mg) was mixed well with sodamide (300mg) and distilled in a kugelrohr. The temperature was raised up to 120°/10mm and later up to 150°/0.02mm. No distillate was obtained. (cf. page 32, compound V).

2. *Reduction*: Acid III (400mg) was reduced with hydrogen using platinum catalyst in alcohol medium at room temperature. The reduction was complete in half an hour. Four moles of hydrogen were used up as calculated. Alcohol was evaporated and the residue crystallised from warm water and recrystallised from the same solvent. The crystals melted at 81° and were identical with dipropylglycolic acid — compound IV.[43]

Found:	C: 59.80%	Calculated for	C: 60.00%
	H: 9.88%	IV $C_8H_{16}O_3$:	H: 10.00%

3. *Reactions with diazomethane*: Acid III (150mg) was dissolved in dry ether and the solution was kept in contact with diazomethane (48mg in 3cc ether) at room temperature for two hours. The oil obtained on removal of the solvent was distilled under high vacuum.

ca. 100mg (compound VI) 60°/0.02mm . . . pale-yellow oil

	C: 64.51%	Calculated for	C: 65.06%
Found:	H: 6.15%	compound VI	H: 6.02%
	methoxyl: 18.69%	$C_9H_{10}O_3$:	methoxyl: 18.60%

3-a. *Pyrazole derivative*: Acid III (500mg) dissolved in 30cc ether was kept in contact with a large excess of ethereal diazomethane at room temperature for three days. Ether was evaporated, more ethereal diazomethane was added and the reaction mixture kept at room temperature for three days more. The process was repeated once again and the heavy yellowish oil obtained after evaporation of the solvent was distilled under vacuum. The distillate was treated with saturated bicarbonate solution and extracted with ether, dried over anhydrous magnesium sulphate and the solvent removed. The oily residue so obtained was distilled under high vacuum and two fractions were collected.

Fraction I: 300mg. ... 60°/0.015mm ... pale-yellow oil

Found :	C: 64.90%	Calculated for compound VI $C_9H_{10}O_3$:	C: 65.06%
	H: 6.22%		H: 6.02%
	methoxyl: 18.80%		methoxyl: 18.60%

Fraction II: 100mg of yellow oil, distilling at 100°/0.015mm. The oil was crystallised from benzene as white crystals melting at 100°. The compound was re-crystallised twice from the same solvent.

M.P : 104°-105°. On sublimation, the melting point was 107°. Analysis of this compund :

Found :	C: 57.69%	Calculated for VII $C_{10}H_{12}O_3N_2$:	C: 57.69%
	H: 5.82%		H: 5.76%
	N: 12.90%		N: 13.50%
	methoxyl: 15.09%		methoxyl: 14.90%

4. *Conversion of (III) into its tricarboxylic acid*: One gram of acid III was dissolved in ether (20cc) and benzene (100cc) was added to it. Ethyl magnesium bromide (30cc) solution was added in drops to the acid solution during forty-five minutes with stirring. The reaction temperature remained at 50°. The pale-yellow solution of the Grignard complex was cooled and well mixed in a rotating

autoclave with powdered dry ice (30gm). The reaction product was kept under fifty-two atmospheres for forty-eight hours. Later, the product was pipetted into a separating flask, acidified and extracted several times with ether, saturating the water layer with salt.

The ether layer was shaken twice with saturated sodium bicarbonate solution and the bicarbonate extract acidified. The aqueous layer was extracted with ether, saturating the aqueous layer with salt. The ether extract was washed, dried over anhydrous magnesium sulphate and evaporated. The residue (700mg of oil) solidified on addidition of carbon tetrachloride to it. The solid was crystallised from chloroform. The crystals had a melting point between 95°–100°. They were sublimed at 70°/0.01mm. The sublimate melted at 103° and was identical with compound III. The carboxylation was not a success in this case (cf. page 33).

Carboxylation was repeated with another compound, namely, with XXII, page 11 (the condensation product of β-ionone and propargyl bromide). Ethyl magnesium bromide (70cc, previously titrated) was added during one and half hours to 5gm of XXII. The reaction product was refluxed for two hours, cooled and mixed with one kilogram of powdered dry ice in an autoclave. The reaction product was kept under 30–40 atmospheres for forty-eight hours, stirring with a magnetic stirrer for twenty-four hours. Later, it was decomposed with acid, extracted with ether, and ether layer shaken with saturated bicarbonate solution. The bicarbonate solution was neutralised with dilute acid and extracted with ether. There was no residue on evaporation of the solvent. However, the starting material, (XXII) was recovered by working up the neutral aqueous layer (5gm).

Attempts at carboxylation of dipropargylglycolic acid (III) and compound XXII (page 11) were not successful.

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Curriculum vitae

I, Ramaswamy, S., a citizen of India, was born in Elur, South India, on the 13th February, 1929. I took my B.Sc. degree in chemistry from the University of Madras in 1949. In April, 1950 I joined the University of Zurich and after finishing my pre-doctorate work, I started the foregoing work for Ph.D. in April, 1951 under the guidance of Professor (Dr.) Paul Karrer and completed it in August 1953.

In the summer vacation of 1950, I worked at the Pregl's Laboratory in Graz, Austria, for six weeks and acquainted myself with micro-analytical techniques. From 15th February upto the middle of April, 1951 I worked at the "Institut Pasteur", Paris. In 1952, I took part in a summer training course for chemists for four weeks given by M/s. Badische Anilin-und Sodafabrik, in Ludwigshafen a/Rhein, Germany. I had also the opportunity to work in the analytical laboratories of M/s. Ciba Ltd., Basle, for ten weeks starting from September, 1953.

On 16th November 1953, I had the privilege to be employed by M/s. Hoffmann-La-Roche & Co. Ltd., Basle, as a Scientific Collaborator. I worked for this firm in Switzerland as well as in India (under M/s. Voltas Ltd.) until November 1956. In December 1956, I joined M/s. Thio-Calcin Co., P.B. No. 904, Madras 20, a pharmaceutical firm owned by my father.

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